

Listing of the Claims

This listing of the claims replaces all the prior versions and listings of the claims.

1. (Currently amended) A method of prolonging expression of a heterologous gene encoding a prodrug activating enzyme in a neoplastic cell transduced with a vector encoding the prodrug activating enzyme comprising
 - a) transducing the neoplastic cell with a vector encoding an apoptosis inhibiting agent.
2. (Cancelled)
3. (Currently amended) The method of claim 1 further comprising contacting the transduced neoplastic cell of step a) with a prodrug.
4. (Cancelled)
5. (Currently amended) The method of claim [[4]] 1, wherein the apoptosis inhibiting agent is a caspase pathway inhibiting agent.
6. (Previously presented) The method of claim 5, wherein the caspase pathway inhibiting agent is selected from the group consisting of p35, p49, CrmA, XIAP, hIAP1, hIAP2, Naip, Bruce, Survivin, pIAP, CiIAP, OpIAP/CpIAP/AcIAP, ASFAP, DIAP1, DIAP2, CeIAP1, CeIAP2, SpIAP, ScIAP, Bcl-2, Bcl-XL, and McI-1.
7. (Original) The method of claim 3, wherein the prodrug activating enzyme is selected from the group consisting of cytochrome P450, NADPH-P450 reductase, thymidine kinase, cytosine deaminase, nitroreductase, thymidine phosphorylase, purine nucleoside phosphorylase, alkaline phosphatase, carboxypeptidase A, carboxypeptidase G2, linamarase, beta-lactamase, xanthine oxidase, guanine phosphoribosyl transferase (GPT), deoxycytidine kinase, uracil phosphoribosyltransferase, carboxylesterase, and folylpolyglutamate synthetase.

8. (Original) The method of claim 3, wherein the prodrug is selected from the group consisting of cyclophosphamide (CPA) and other P450 prodrugs including bioreductive agents activated by P450 and/or NADPH-P450 reductase; ganciclovir, acyclovir and their analogs; 5-fluorocytosine; CB1954 and other aromatic nitro prodrugs; 5'-deoxy-5-fluorouridine; 6-methylpurine-2'-deoxynucleoside; etoposide phosphate; methotrexate-(phenyl)alanine; benzoic acid mustard-glucuronide; amygdalin; cephalosporin-mustard carbamate; xanthine; 6-thioxanthine; cytosine arabinoside; 5-fluorouracil; irinotecan (CPT-11); edatrexate.
9. (Original) The method of claim 3, wherein the prodrug activating enzyme is cytochrome P450 and the prodrug is cyclophosphamide or ifosfamide.
10. (Original) The method of claim 9, wherein the prodrug-activating cytochrome P450 enzyme is selected from the group consisting of CYP 1A1, 1A2, 1B1, 2A6, 2B1, 2B6, 2B11, 2C3, 2C5, 2C6, 2C7, 2C8, 2C9, 2C11, 2C18, 2C19, 3A1, 3A2, 3A3, 3A4, 3A5 and 3A7.
11. (Currently amended) A method of increasing the concentration of a chemotherapeutic drug in, or in the vicinity of, a target neoplastic cell in a mammal in need thereof comprising the steps of:
 - a) transducing the target neoplastic cell with a first vector comprising a nucleic acid encoding a prodrug activating enzyme;
 - b) transducing the target neoplastic cell with a second vector comprising a nucleic acid encoding an apoptosis inhibiting agent; and
 - c) subjecting the mammal to a prodrug that is activated by the prodrug activating enzyme of step a).
12. (Cancelled)

13. (Currently amended) A method of increasing the concentration of a chemotherapeutic drug in, or in the vicinity of, a target neoplastic cell in a mammal in need thereof comprising the steps of:
 - a) transducing the target neoplastic cell with a vector comprising a nucleic acid encoding a prodrug activating enzyme and a nucleic acid encoding an apoptosis inhibiting agent; and
 - b) subjecting the mammal to a prodrug that is activated by the prodrug activating enzyme of step a).
14. (Previously presented) The method of claim 11, wherein the apoptosis inhibiting agent is expressed under control of a regulatable promoter.
15. (Previously presented) The method of claim 1, wherein the vector comprising a nucleic acid encoding an apoptosis inhibiting agent further comprises a factor that promotes apoptosis expressed under control of a regulatable promoter.
16. (Original) The method of claim 15, wherein the factor that promotes apoptosis is selected from the group consisting of Smac/Diablo a caspase, p53, Bax, Bak, Bcl-Xs, Bad, Bik, Bid, apoptosis inducing factor, and anti-sense or siRNA directed against the apoptosis inhibiting agent, an IAP or other anti-apoptotic factor.
17. (Previously presented) The method of claim 11, wherein the vector comprising a nucleic acid encoding an apoptosis inhibiting agent further comprises a death receptor ligand expressed under control of a regulatable promoter.
18. (Original) The method of claim 17, wherein the death receptor ligand is selected from the group consisting of TNF α , Trail and Fas ligand.
- 19-30. (Cancelled)
31. (Previously presented) The method of claim 13, wherein the apoptosis inhibiting agent is expressed under control of a regulatable promoter.

32. (Previously presented) The method of claim 13, wherein the vector comprising a nucleic acid encoding an apoptosis inhibiting agent, further comprises a factor that promotes apoptosis expressed under control of a regulatable promoter.
33. (Previously presented) The method of claim 13, wherein the vector comprising a nucleic acid encoding an apoptosis inhibiting agent further comprises a death receptor ligand expressed under control of a regulatable promoter.
- 34-36. (Cancelled)
37. (Currently amended) A method for increasing vector spread in a host comprising administering to the host a vector system, wherein the vector system comprises a replicating vector encoding a prodrug activating enzyme and a non-replicating vector encoding an apoptosis inhibiting agent wherein the replicating vector encoding the prodrug activating enzyme is administered prior to, concurrently with or after the administration of the non-replicating vector encoding the apoptosis inhibiting agent.
38. (Currently amended) A method of increasing the concentration of a chemotherapeutic drug in, or in the vicinity of a target neoplastic cell in a tumor in a mammal affected with the tumor comprising the steps of:
- a) transducing the target neoplastic cell with a first vector comprising a nucleic acid encoding a prodrug activating enzyme;
 - b) transducing the target neoplastic cell with a second vector comprising a nucleic acid encoding an apoptosis inhibiting agent; and
 - c) subjecting the mammal to a prodrug that is activated by the prodrug activating enzyme of step a).